PATENT COOPERATION TR. CORRECTED VERSION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/000800	11.01.2005	16.01.2004

International Patent Classification (IPC) or both national classification and IPC
A61K49/10, A61K49/18, A61K51/04

Applicant
CARNEGIE MELLON UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	ESTANOL, I Telephone No. +49 89 2399-8647

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/000800

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	15,16
	No:	Claims	1, 2, 4, 13, 17-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV.

The separate inventions/groups of inventions are:

Invention 1:
Claim 1: Method for labelling a cell with a fluorocarbon imaging reagent.
Invention 2:
Claim 21: An imaging reagent with specific fluorocarbons.
Invention 3:
Claim 26: Linear fluorocarbon derivatized with a detection moiety or a hydrophilic moiety or a targeting moiety or a cellular uptake moiety.
Invention 4:
Claim 30: An emulsion comprising a perfluoroether with a particle size ranging from 10 to 500 nm.
Invention 5:
Claim 32: A method for detecting a cell in a subject comprising administering a cell labelled with a fluorocarbon imaging reagent and examining by NMR technique.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The common concept of independent claims 1, 21, 26, 30 and 32 is the fluorocarbon imaging reagent. This common concept is not new over the prior art D1 or D2 or D3 or D4 or D5 or D6 or D7 or D8 or D9 or D10.
Thus, the present application lacks unity, contrary to Rule 13 PCT. Consequently, the search report only covers the subject-matter of invention n°1.

Re Item V.

1 Reference is made to the following documents:

D1 : WO 94/21303 A (ALLIANCE PHARMACEUTICAL CORP) 29 September 1994 (1994-09-29)
D2 : Forstrom LA et al., "18F-FDG labelling of human leucocytes", Nuclear magnetic communications, 2000, 21 (7), 691-694
D3 : US 5114703
D4 : EP 0 307 863 A (AIR PRODUCTS AND CHEMICALS, INC) 22 March 1989 (1989-03-22)

2 Independent claim 1

Novelty:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new over D1 or D2 in the sense of Article 33(2) PCT.

Document D1 discloses method for labelling a cell ex vivo (page 5, lines 30-31) using a fluorocarbon such as (CF3)2CFO(CF2CF2)2OCF(CF3)2 (page 3, lines 31-37) in an emulsion (page 2, line 37). The cell of D1 is labelled with the fluorocarbon by internalizing the reagent or by associating it extracellularly (page 7, lines 20-21).

Document D2 discloses a method for labelling leucocytes ex vivo with 18F-fluorodeoxyglucose.

Inventive step
The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claim 1 does not involve an inventive step in the sense of Article 33(3)PCT.

Document D1 is considered to represent the most relevant state of the art to the subject matter of claim 1.

3 Dependent claims 2-20
Dependent claims 2-20 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, the reasons being as follows:
- Fluorocarbon emulsions having a particle size of or below 500 nm are disclosed in D3 (col. 8, lines 50-59).
- The cell of D1 is labelled with the fluorocarbon by internalizing the reagent or by associating it extracellularly (page 7, lines 20-21).
- The fluorocarbon used in D1 is inter alia (CF3)2CFO(CF2CF2)2OCF(CF3)2 (page 3, lines 31-37).
- The cells labelled in D1 or D2 are from the RES system or leucocytes, respectively.
- Perfluoro-crown ether are disclosed in D4 as providing the same effects.

4. Furthermore, claim 1 does not disclosed under which conditions the fluorocarbon imaging reagent becomes associated with the cell. Thus, the essential features to carry out the invention are missing.